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# Statin-Induced Rhabdomyolysis, Acute Kidney Injury, and Hepatitis Leading to Death

Authors' Contribution:  
Study Design A  
Data Collection B  
Statistical Analysis C  
Data Interpretation D  
Manuscript Preparation E  
Literature Search F  
Funds Collection G

ABCDEF 1 **Mouhand F.H. Mohamed**  
EG 1 **Omar K. Salameh**  
EFG 1,2 **Abazar A.M. Saeed**

1 Department of Internal Medicine, Hamad General Hospital, Hamad Medical Corporation, Doha, Qatar  
2 Weill Cornell Medicine, Doha, Qatar

**Corresponding Author:** Mouhand F.H. Mohamed, e-mail: [dr.m.oraiby@hotmail.com](mailto:dr.m.oraiby@hotmail.com)  
**Conflict of interest:** None declared

**Patient:** Male, 67  
**Final Diagnosis:** Statin-induced rhabdomyolysis and hepatitis  
**Symptoms:** Dark urine • muscle pain • muscle weakness • pale stool • yellowish skin discoloration  
**Medication:** Atorvastatin  
**Clinical Procedure:** Dialysis  
**Specialty:** General and Internal Medicine





**Objective:** Unusual or unexpected effect of treatment  
**Background:** Statins are effective in reducing cardiovascular morbidity and mortality, and are generally safe, but can rarely result in devastating adverse effects. With the increasing indications and prescriptions of statins, rare adverse effects are more likely to be seen and reported. Unfortunately, there are no accurate predictive tools to estimate the risk of developing these adverse effects. Post-marketing surveillance helps in collecting data on adverse effects and assists in developing better prognostic tools that can help physicians make better therapeutic decisions.

**Case Report:** A 67-year-old man was admitted to our hospital with generalized body aches, muscle weakness, jaundice, dark urine, and decreased urine output. He was started on atorvastatin 4 months prior to presentation after having an episode of myocardial infarction, and he was diagnosed as having statin-induced hepatitis, rhabdomyolysis, and acute kidney injury. A basic workup excluded other possible causes. The patient, unfortunately, died of unknown causes on day 6 after admission, and an autopsy was not performed.

**Conclusions:** Statins are effective and safe but can result in rare and dangerous adverse effects. Physicians should counsel their patients on proper identification and timely reporting of such adverse effects. Physicians also should be encouraged to report any adverse drug reactions and help in promoting post-marketing surveillance studies. The present case is an excellent example of the importance of these studies, especially for commonly-used drugs.

**MeSH Keywords:** Acute Kidney Injury • Dialysis • Drug-Induced Liver Injury • Hydroxymethylglutaryl-CoA Reductase Inhibitors • Rhabdomyolysis • Hepatitis

**Full-text PDF:** <https://www.amjcaserep.com/abstract/index/idArt/914707>

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## Background

Physicians prescribe statins widely to prevent cardiovascular morbidity and mortality [1–3]. In 2008, twenty-five million patients were on statin medications [4], and this number is likely higher now given the growing number of statins indications. Statin use is not without risks, and devastating consequences have been reported.

Here, we present the unfortunate consequences of statin use in a patient who presented to our hospital (Hamad Medical Corporation) in Qatar and discuss the management and outcome, as well as stressing the importance of post-marketing surveillance studies and reporting adverse drug effects.

## Case Report

We report the case of a 67-year-old Middle Eastern male, smoker, known to have successfully treated hepatitis C virus, and coronary artery disease diagnosed 4 months before admission after stent placement. He was on dual antiplatelet and atorvastatin 40 mg. He presented to our hospital with increasing generalized body aches and muscle weakness. His weakness started 2 months before presentation and was mainly involving his legs, but increased in the last week. He also reported a few days history of yellowish sclera discoloration, dark urine, pale stool, itching, and oliguria. A few days before

admission, he presented to the Emergency Department with an episode of blood mixed in stool, and he was found to have a small anal fissure. He had no recurrence of bleeding after that. On examination, he was afebrile, with a blood pressure of 120/70 mmHg, with normal oxygen saturation. He was jaundiced, in no acute distress, had tenderness in lower limbs with weakness, and limited mobility. Cardiac, pulmonary, and abdominal examinations were grossly unremarkable.

Laboratory workup (Table 1) revealed raised transaminase enzymes, alkaline phosphatase (ALP), bilirubin, and the international normalized ratio (INR). Creatinine kinase (CK) was markedly elevated, urine dipstick positive for blood (which was absent on microscopy suggestive of myoglobinuria), and raised urea and creatinine levels. Hepatitis C, cytomegalovirus, and adenovirus polymerase chain reaction (PCR) tests were negative. Ceruloplasmin and alpha-1-antitrypsin levels were normal. Antinuclear antibodies (ANA) and anti-myeloperoxidase antibody of 13 IU/ml (<10 IU/ml) were weakly positive. On repeat testing, ANA was negative, and the Rheumatology team disregarded this result given that repeat testing is negative with absence of other features of autoimmune diseases. An ultrasound scan of the abdomen showed a normal-sized liver (14 cm) with increased echogenicity, with spleen size of 13 cm and normal portal vein size.

After excluding other causes of hepatitis, as well as other causes of rhabdomyolysis like trauma and viral infections,

**Table 1.** Patient's significant lab values before and after admission to the hospital.

Labs	4 months before admission	10 days before admission	Day 1	Day 4	Day 6
White blood cells (WBC) [4.00–11.0×10 <sup>9</sup> /L]	6.8	5.2	8.9	13.2	16.5
Hb [13–17 gm/dl]	15.9	15.5	15.1	14.4	14.3
Platelets [150–400 10 <sup>9</sup> /liter]	180	190	164	174	187
INR	1.1	1.6	1.6	1.4	NA
Bilirubin [3.4–20.5 umol/liter]	7	123	164	166	211
Alanine aminotransferase (ALT) [0–55 unit/liter]	26	1325	986	767	834
Aspartate aminotransferase (AST) [5–34 unit/Liter]	35	1280	1352	1271	1612
ALP [40–150 unit/liter]	69	249	278	228	211
Creatinine [64–110 umol/liter]	73	122	501	746	865
Potassium [3.6–5.1 mmol/liter]	3.9	5	4.8	4.8	6.4
CK [30–200 U/Liter]	NA	NA	18 267	26 774	>22.000
Arterial blood gases pH [7.35–7.45]	NA	NA	7.41	7.33	7.31

NA – not applicable.

we diagnosed our patient as a case of probable statin-induced acute hepatitis and rhabdomyolysis with acute kidney injury (the Naranjo scale was used to estimate the drug-related probability [5]). The patient was resuscitated with intravenous fluids, with monitoring of urine output, CK level, and liver enzymes. Despite an initial decrease in his aminotransferases, his urine output and creatinine level did not improve, with rising potassium level. He was started on hemodialysis on the sixth day of admission. A few hours after dialysis, the patient, unfortunately, had a cardiac arrest, and efforts to resuscitate him were unsuccessful. There were no signs of infection. Possible causes of death were electrolytes disturbances aggravating arrhythmia (potassium level post-dialysis was 5.4 mmol) and an undiagnosed myocardial infarction. The cause of death was not possible to determine because an autopsy was not performed.

## Discussion

Use of statins (3-Hydroxy- 3- Methylglutaryl coenzyme (HMG-CoA) inhibitors) has dramatically decreased cardiovascular diseases morbidity and mortality [1–3]. They are generally safe and effective [6,7]; however, risks with their use can occur, and these risks are difficult to quantify and to anticipate. Results from post-marketing studies [8] revealed that the overall adverse event rate is less than 0.5% and the rate of muscle injury is less than 0.1%, but the actual incidence of adverse events is not known given that post-marketing surveys are flawed by under-reporting.

Rhabdomyolysis and hepatitis are known complications of statins; however, their combination with this severity is uncommon and this combination has been reported only a few times in the literature. We found 2 cases resembling our case, in which significant statin-induced combined liver and renal injury occurred; in both cases, the authors used the Naranjo probability scale to estimate the probability of adverse drug reaction [5].

Hadim Akoglu et al. [9] reported the first case in 2007, in which a 56-year-old woman with a history of hyperlipidemia and no other comorbidities was started on a combination of Fluvastatin (80 mg/day) and gemfibrozil (1200 mg/day). One month later, she was admitted and was found to have acute renal failure (due to rhabdomyolysis) and acute hepatocellular injury. A favorable outcome occurred after stopping probable offending agents, with normalization of her lab results, and she was discharged 15 days after admission.

In 2009, Muthuram et al. [10] reported the case of a 77-year-old man diagnosed with aortic stenosis, whose atorvastatin dose was increased from 40 mg to 80 mg 6 months before presentation. He presented with acute hepatitis, rhabdomyolysis,

and acute renal failure. The probability score suggested that the culprit was the atorvastatin; unfortunately, the patient developed multiorgan failure and died 2 weeks later.

In the first case [9], there were no apparent risks associated with statin use. In the second case, the age and the aortic stenosis history may have contributed; however, it is difficult to know based on baseline characteristics which patients might develop adverse drug effects given the lack of accurate prognostic tools. Further research on this topic is needed, as are post-marketing studies.

Statins pre-marketing studies (phase II, III) revealed morbidity and mortality reduction [1–3]. Pre-marketing studies expose a relatively small sample to intervention in controlled settings. These studies are mainly powered to detect efficacy of the drug or intervention, but are not powered to detect adverse effects, especially the rare ones, limiting the detection of uncommon adverse effects.

For an adverse effect, for example, that has an incidence of 1: 3000, a study conducted on 2000 participants may fail to show the adverse effect and hence falsely conclude that the intervention is safe; such adverse effects may emerge after marketing. This example shows this inherent defect of pre-marketing studies and thus the importance of proper post-marketing studies with regards to statins or any other drug [11].

Statins use has demonstrated significant efficacy when used in appropriate patients in whom benefits outweigh risks, but our case reminds us of the significant toxicity that can accompany this commonly prescribed drug. As physicians, we should be aware of the adverse reactions of statins and know how to recognize them. Physicians should individualize the decision to start statins in atypical scenarios where statins use may not have strong clinical grounds. At the commencement of statins, we believe that clinicians should have a lengthy conversation with patients explaining not only the tremendous expected benefits, but also the associated risks and how to recognize and detect them in a timely manner.

We also encourage clinicians to contribute to the pool of research by proper voluntary reporting of all adverse drug reactions associated with statins or any other drug. More emphasis on post-marketing studies is needed, using active and passive methods to encourage the reporting of adverse drug reactions.

## Conclusions

Statins are for the most part effective and safe; but, can rarely lead to devastating adverse effects, as highlighted by our case.

There are no accurate predictive tools to anticipate the risk of statin-induced adverse effects.

Physician and patients should be able to recognize adverse effects promptly, and the decision to start statins should be made an agreement with the patient after counseling on recognition and reporting of adverse effects. More emphasis is needed on improving post-marketing studies; this case is an excellent example of the importance of these studies, especially for commonly prescribed medications.

## References:

1. Taylor F, Huffman MD, Macedo AF et al: Statins for the primary prevention of cardiovascular disease. *Cochrane Database Syst Rev*, 2013; (1): CD004816
2. Colhoun HM, Betteridge DJ, Durrington PN et al: Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): Multicentre randomised placebo-controlled trial. *Lancet*, 2004; 364(9435): 685–96
2. Vrečer M, Turk S, Drinovec J, Mrhar A: Use of statins in primary and secondary prevention of coronary heart disease and ischemic stroke. Meta-analysis of randomized trials. *Int J Clin Pharmacol Ther*, 2003; 41(12): 567–77
4. Mitka M: Expanding statin use to help more at-risk patients is causing financial heartburn. *JAMA*, 2003; 290(17): 2243–45
5. Naranjo CA, Busto U, Sellers EM et al: A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther*, 1981; 30(2): 239–45
6. Maji D, Shaikh S, Solanki D, Gaurav K: Safety of statins. *Indian J Endocrinol Metab*, 2013; 17(4): 636–46
7. Armitage J: The safety of statins in clinical practice. *Lancet*, 2007; 370(9601): 1781–90
8. Evans M, Rees A: Effects of HMG-CoA reductase inhibitors on skeletal muscle: Are all statins the same? *Drug Saf*, 2002; 25(9): 649–63
9. Akoglu H, Yilmaz R, Kirkpantur A et al: Combined organ failure with combination antihyperlipidemic treatment: A case of hepatic injury and acute renal failure. *Ann Pharmacother*, 2007; 41(1): 143–47
10. Rajaram M: Hepatitis, rhabdomyolysis and multi-organ failure resulting from statin use. *BMJ Case Rep*, 2009; 2009: bcr0720080412
11. Berlin JA, Glasser SC, Ellenberg SS: Adverse event detection in drug development: Recommendations and obligations beyond phase 3. *Am J Public Health*, 2008; 98(8): 1366–71

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## Conflict of interest

None.